PATENT
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Applicant:	Pastorello et al.	Confirmation No.:	5027
Serial No.:	10/580,659	Art Unit:	1651
§ 371 Date:	May 26, 2006	Examiner:	A. J. Kosar
Customer No.:	21559		
Title:	COMPOSITE STRUCTURES CONTAINING HYALURONIC ACID THE DERIVATIVES THEREOF AS NEW BONE SUBSTITUTES AND GRAFTS		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY TO RESTRICTION REQUIREMENT

In reply to the Restriction Requirement that was mailed in connection with the above-captioned case on November 15, 2007, applicant makes the following election with traverse.

Group Election:

Applicant elects group (I), i.e., claims 1-49, 61, and 63 (in part), and claims 50-53, drawn to a multi-layer composite material containing a pharmacologically/biologically active ingredient. Applicant further submits that claims 54-56 should be examined with group I, as nothing in these claims excludes the species elected below.

Species Election:

1. The species of material

Applicant elects the hyaluronic acid ("HA") ester and in particular the benzyl ester as the derivative material to be used to construct the inner matrix and the external layer.

2. The species of ceramic material to be used in the matrix

Applicant elects biocompatible and biodegradable ceramics in particular tribasic calcium phosphate as the ceramic material to be used in the matrix.

3. The species of polymer

Applicant elects the HA benzyl ester with a percentage of esterification of from 55 to 100% listed in claim 43 as the species of polymer to be used for making the inner matrix more compact.

4. The species of pharmacologically active agent or biologically active agent

The species of active ingredient to be elected shall be an osteoinductive factor.

The fifth species is not applicable to the elected group.

The elected species read on claims 1-17, 19-39, 42-56, 61, and 63.

Traversal:

The basis for restriction provided by the Office is that the claims do not possess a special technical feature that makes a contribution over the prior art, namely Pavesio (WO 02/070030). Applicant disagrees.

NOVELTY

The invention relating to a **multi-layer** composite material containing:

- an inner matrix comprising:
  - (i) hyaluronic acid or a derivative thereof, and
  - (ii) a matrix of demineralised bone, and/or biocompatible and biodegradable ceramics, and/or bone of autologous or allogenic or animal origin,
- **at least one layer** of a hyaluronic acid derivative

is **novel** over Pavesio.

Pavesio discloses a three-dimensional bilayer composite material formed by:

- **as the first layer**: a three dimensional hyaluronic scaffold formed of a hyaluronic acid derivative enclosing empty spaces created by communicating pores and/or a tangle of fine fibers or microfibers with or without cells, and
- **as the second layer**: a porous three-dimensional matrix constituted by a ceramic material (see page 7, lines 9-16, claim 1 and more specifically example 1).

The above layers are joined together by using a fibrin glue.

The multilayer composite as claimed in claim 1 differs from that disclosed by Pavesio:

- unlike the bi-layer composite disclosed by Pavesio, contemplating the first layer being formed by the sole ceramic material, the inner matrix of the present invention

contains both (i) the ceramic material **and** (ii) hyaluronic acid and derivatives, which **form together a single layer**.

- **Only** the second layer in the composite material as claimed in claim 1 is **formed by a hyaluronic acid derivative** that may be fixed with **fibrin glue to the inner matrix**.

According to Pavesio, the bi-layer composite material is used in the preparation of engineered osteochondral grafts, containing both a cartilage part and a bone part that are **separate** for the repair of structurally integrated **osteochondral** tissue in vivo (see page 7, lines 9-18; claim 1).

By contrast, the multilayer composite material of claim 1 is used in the preparation of only **bone** substitutes or grafts or formation of bone tissue, e.g., in oncological, orthopaedic, and especially in spinal surgery wherein **it is utilized in the fusion of two adjacent vertebrae**.

It is therefore evident that the material to be used for the regeneration of bone tissue must be structurally different from a material to be used for the regeneration of an osteochondral tissue namely an **articular** tissue like that disclosed by Pavesio.

UNOBVIOUSNESS

The present invention is also unobvious over Pavesio. As pointed out in the "Background of Invention" in the instant Description, there are various surgical techniques and methods of fusing two adjacent vertebrae, but they all involve the introduction/application of a bone graft, generally between two vertebrae, or bone substitutes of various kinds of different shapes and sizes, such as pins, plugs, or small plates fitted in the intervertebral spaces to prevent collapse and assist fusion.

These measures are aimed to:

- maintain correct alignment between the two vertebrae;
- maintain and reconstruct the intervertebral space;
- consolidate fusion; and
- eliminate pain caused by compression of the nerve root due to slipping or herniation of the disk.

It is known that spinal fusion may also require **additional fixing at the back** of the two vertebrae, using rigid metal instruments of various kinds and sizes, such as screws, plugs, pins, plates, or intervertebral connectors in various materials, with or without a screwable thread (for example, titanium), to prevent the vertebrae from slipping on one another with consequent compression and loss of alignment, while fusion is established.

These devices do not undergo resorption so they generally remain at the site of implantation until they are surgically removed once fusion is complete. The vertebrae can be fused in the intervertebral space and/or to the front between the two adjacent vertebral bodies and/or to the back between adjacent transverse processes, laminae, or between other posterior elements of the vertebrae, according to the pathology that the surgery in question is intended to treat

Solid fusion is generally achieved by grafting autologous or allogenic bone, both having specific advantages and disadvantages.

Indeed, in the case of autogenous bone, it may prove difficult to find a quantity that is sufficient for the purpose of the graft. Allogenic bone, on the other hand, has less osteoinductive activities.

These difficulties have led to the study and development of bone substitutes of synthetic, semi-synthetic, and bioengineering origin, that is, to the construction of two- and three-dimensional osteoconductive matrices able to induce the migration of cells within their structure for the subsequent formation of bone.

Research was then focused on the study of the physiological mechanisms involved in bone repair and regeneration.

The ability of bone to regenerate when damaged is due to certain features:

- osteogenic capacity;
- osteoinductive capacity; and
- osteoconductive capacity.

In spinal surgery, this last property is linked with the presence of a **scaffold fixed to the structures to be fused (without using the aforementioned metal means)** allowing the migration and distribution of both bone progenitor and vascular cells within its structure.

Applicant has unexpectedly found that the multilayer composite as claimed in claim 1 satisfies the above requirements (page 7, line15 - page 8, line 6 of the Specification).

The claimed composition is **osteoinductive, osteogenic, osteoconductive,** and is also able **to be fixed with surgical thread and/or glued with fibrin or other natural or synthetic glues, or using polymers such as hyaluronic acid and the derivatives thereof.**

In addition, this graft is also characterised by having the following **additional** properties:

- it is biodegradable and do not produce any substances that are potentially toxic or that may elicit an inflammatory response by the host organism;

- it can be loaded with cell components of bone marrow, or purified mesenchymal cells (possibly expanded in vitro), undifferentiated, or partially or completely differentiated, in vitro, into osteoblasts and/or osteocytes;
- it can contain pharmacologically and/or biologically active ingredients such as antibiotics, steroid and non-steroid anti-inflammatory drugs, antineoplastic agents, cytotoxic and/or cytostatic agents, antiviral agents, cytokines, and vitamins; and
- it can be made into any shape or size, so that they can be applied surgically wherever a graft is required.

Pavesio's composition as previously pointed out is completely different. As discussed, Pavesio's target is to find a composite material to be used in as an osteochondral graft containing **both a cartilage part and a bone part**, and such a goal is achieved with a bilayer composite material whose first layer is a porous three-dimensional matrix constituted by a ceramic material and the second layer is formed by a porous three-dimensional matrix constituted by a hyaluronic acid derivative (see page 7, lines 9-16, claim 1, and more specifically example 1).

In view of the above, Applicant requests that the election requirement be withdrawn, as the multilayer composite material as claimed in claim 1 satisfies the unity of invention requirements as it is novel and unobvious.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: December 17, 2007

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